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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,344	06/09/2005	Guy Vergnault	28069-608 NATL	3745
35437 7590 06/09/2009 MINTZ LEVIN COHN FERRIS GLOVSKY & POPEO ONE FINANCIAL CENTER BOSTON, MA 02111			EXAMINER YOUNG, SHAWQUA	
			ART UNIT 1626	PAPER NUMBER
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/538,344	<b>Applicant(s)</b> VERGNAULT ET AL.	
	<b>Examiner</b> SHAWQUIA YOUNG	<b>Art Unit</b> 1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 06 August 2008.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-12 and 14-24 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-12 and 14-24 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

Claims 1-12 and 14-24 are currently pending in the instant application.

Applicants have cancelled claim 13 in an amendment filed on August 6, 2008. Claims 1-12 and 14-24 are rejected in this Office Action.

#### **I. *Response to Arguments***

Applicants' arguments, filed on August 6, 2008, relating to claims 1,2,8 and 14-24 as being unpatentable over Stefano (US 5,506,222) in view of Schäfer-Korting et al., ("Delivery of Lipophilic Compounds with Lipid Nanoparticles - Applications in Dermatics and for Transdermal Therapy," in Lipospheres in Drug Targets and Delivery, CRC Press (2005), Claudio Nastruzzi, Editor), in further view DrugBank (<http://redpoll.pharmacy.ualberta.ca/drugbank>) and of references cited in Schäfer-Korting (Reference 9, Mehnert and Maider, "Solid lipid nanoparticles: Production, characterization and applications," Adv. Drug Deliv. Rev. (2001) 47:165-196; and Reference 29, zur Mühlen, et al., "Solid Lipid Nanoparticles for Controlled Drug Delivery," Eur. J. Pharm. Biopharm. (1998) 45:149-155); the rejection of claims 3-5 under 35 USC 103 as being unpatentable over Stefano in view of Schäfer-Korting in further view of Lane and the rejection of claims 6,7 and 9-12 under 35 USC 103 as being unpatentable over Stefano in view of Schäfer-Korting in further view of Hansen and Kirk-Othmer have been fully considered but are not persuasive.

The basis of Applicants' arguments is that the reference Schäfer-Korting can not be used as a 103 prior art reference because it has a publication date of 2005.

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However, the Examiner wants to point out that the Schafer-Korting reference is being used because of a teaching of a limitation which is cited by the reference 9 which is Mehnert and Mader, "Solid lipid nanoparticles: Production, characterization and applications," Adv. Drug Deliv. Rev. (2001) 47:165-196. The Mehnert, et al. reference has a publication date of 2001 which is prior to Applicants' priority date. Thus the reference can be used as a 103 reference and since Applicants have failed to persuasively argue the 103 rejections, each rejection will be maintained.

## **II. *Rejection(s)***

### **Claim Rejections - 35 USC § 103**

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or

described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 2, 8 and 14-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stefano (US 5,506,222) in view of Schäfer-Korting et al., ("Delivery of Lipophilic Compounds with Lipid Nanoparticles - Applications in Dermatics and for Transdermal Therapy," in Lipospheres in Drug Targets and Delivery, CRC Press (2005), Claudio Nastruzzi, Editor), in further view DrugBank (<http://redpoll.pharmacy.ualberta.ca/drugbank>) and of references cited in Schäfer-Korting (Reference 9, Mehnert and Mäder, "Solid lipid nanoparticles: Production, characterization and applications," Adv. Drug Deliv. Rev. (2001) 47:165-196; and Reference 29, zur Mühlen, et al., "Solid Lipid Nanoparticles for Controlled Drug Delivery," Eur. J. Pharm. Biopharm. (1998) 45:149-155).

Regarding claims 1 and 2, the instant Application is drawn to a formulation comprising spironolactone in an oriented crystalline lipid matrix for application to skin or mucosa. Stefano teaches spironolactone for topical application (column 11, claim 1) in a lipid matrix (column 12, claim 2, Substituted unsaturated fatty acids), but is silent regarding oriented crystalline nanoparticles. Schäfer-Korting teaches solid lipid

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nanoparticles (50 to 1000 nm) for topical application (Section 7.2 and Reference 9) having a drug enriched core with a lipid crystal shell, formed as a function of the lipid's melting point and the relative solubilities of the drug and the lipid (page 133, Section 7.6, Figure 7.3, and Reference 29). The drug enriched core is formed when the drug precipitates before the lipid crystallizes. Because spironolactone (7a-acetylthio-3-oxo-17a-pregn-4-ene-21,17-carbolactone) is practically insoluble in water and has a Log P of 4.3 (See Drugbank entry for Spironolactone), the lipid nanoparticulate form of the drug forms such that the lipid crystal shell's hydrophilic "side" would face "outward," because the hydrophobic "side" would face "inward" toward the encapsulated lipophilic spironolactone. Schäfer-Korting citing Mehnert and Milder (at Section 1.2) further teaches that photon correlation spectroscopy is the state of the art measurement technique for particle size determinations of particles in the range of "a few nanometers to 3  $\mu$ m."

Because enhanced skin permeation (Schäfer-Korting, section 7.10.2) occasioned by use of the nanoparticulate dosage form, obviates the need for additional formulation components (e.g., Stefano's permeation enhancers) it would have been obvious to the person of ordinary skill in the art at the time the invention was made to have combined the formulation taught by Stefano with the liquid crystalline nanoparticulate lipid taught by Schäfer-Korting to obtain a topical dosage form of spironolactone with bioavailability resulting from the use of nanoparticulates rather than formulated permeation enhancers. Regarding claims 8, 14-19, 23 and 24, Schäfer-Korting and Stefano are discussed above, with Stefano teaching the use of topical spironolactone compositions to treat the

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effects of increased androgenic activity including acne and hirsutism (Abstract). These topical formulations comprise glyceryl monoesters, e.g. glyceryl monostearate (column 6, line 26), which are inherently crystalline under certain conditions of temperature, and other components of a cosmetically suitable cream base (column 4, lines 54 to 63) with additional excipients designed to promote drug delivery at the active site within the skin strata in order to obtain a therapeutic effect (column 5, Example 1 et seq.). Thus, it would have been obvious to the artisan of ordinary skill to combine the topical spironolactone formulation and dosing information of Stefano with the skin permeation enhancing nanocrystallinity of Schäfer-Korting to treat the effects of increased androgenic activity (e.g., acne and hirsutism) in patients with a need for such treatment using a topical preparation.

Regarding claim 20, combining the skin permeation enhancing oriented crystalline network system of Schäfer-Korting with the "incorporated substance for use in topical treatment of acne" (e.g., spironolactone) as taught by Stefano would have been obvious to a person of ordinary skill in the art to obtain a topical dosage form with a bioavailable active ingredient resulting from the use of nanoparticulates rather than additional formulation components.

Regarding claims 21 and 22, Schäfer-Korting, Schäfer-Korting citing Mehnert and Meider, and Stefano are discussed above, but they do not teach specific particles in the size range of from 300 to 900 nanometers. Schäfer-Korting teaches (Section 7.10.2.) that drug penetration into the skin strata is strongly related to particle size with "particles

smaller than 400 nm [proving] to be most potent." The adjustment of particular conventional working conditions (e.g., determining result effective particle sizes beneficially taught by the cited references, especially within the broad ranges recited in claims), as well as affecting desired skin penetration (bioavailability of the active ingredient), is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the artisan of ordinary skill. Accordingly, this type of modification would have been well within the purview of the person of ordinary skill in the art and no more than an effort to optimize results.

Claims 3-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stefano in view of Schäfer-Korting in further view of Lane ([http://ches.ua.edu/departments/nhm/faculty/lane/nhm454/McWCh 11 & 12fats.pdf](http://ches.ua.edu/departments/nhm/faculty/lane/nhm454/McWCh%2011%20&%2012fats.pdf)). Stefano and Schäfer-Korting are discussed above with Stefano further teaching glycerol monoesters (e.g., glyceryl monostearate, column 6, line 26), but they are silent regarding lipid crystallization temperature. Lane teaches lipids with a crystallization temperature in the recited range (70°C, page 1, lower right), and further teaches I3-crystal of the monoglycerides of C~8 fatty acids (pages 2-3). Adjustment of crystallization temperature by judicious selection of formulation components such as these glyceryl monoesters yields an extent of crystallinity useful in topical formulations for transporting spironolactone through the skin strata, and would have been well within the purview of a person of ordinary skill in the art at the time the invention was made.



Claims 6, 7 and 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stefano in view of Schäfer-Korting in further view of Hansen (US 6,228,383 B 1) and Kirk- Othmer (Kirk-Othmer Encyclopedia of Chemical Technology (2001), Wiley Interscience.

Regarding claims 6 and 7, Stefano and Schäfer-Korting are discussed above, but are silent regarding the solvent in which the nanoparticulate is formed. Hansen teaches that the lipid crystals are formed from polar liquids such as water and glycerol (column 6, lines 23 to 53), and that the lipid crystals are comprised of glyceryl monoesters of C<sub>18</sub> fatty acids (Id.). Accordingly, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to have combined the nanoparticulates taught by Stefano and Schäfer-Korting with the solvent and lipid formulation components (specifically their inherent physical properties) taught by Hansen in order to obtain a product with the physical properties necessary to effect a solid state product at a temperature range suitable for typical topical cosmetic preparations.

Regarding claims 9-12, Hansen and Schäfer-Korting are discussed above with Hansen further teaching that the composition may be characterized as a suspension (column 14, line 46, thus in view of Schäfer-Korting a "nanosuspension") and that it further comprises a stabilizer (e.g., emulsifying agent, antioxidant, preservative, solubilizing agent, column 14, lines 52-67), which would have been an obvious addition to the formulation in order to

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maintain the suspension over the time and temperature ranges required to yield a useful product.

Hansen and Schäifer-Kortingare both silent regarding sodium docusate as a stabilizer per se, but the person of ordinary skill in the art would recognize the term "stabilizer" as referring to any of a number of classes of compounds including surface active agents. Hansen teaches "solubilizing agents" (column 14, line 65), and as indicated in Kirk-Othmer, sodium docusate is a surface active agent (i. e., solubilizing agent) used in pharmaceuticals ("Gastrointestinal agents, page 16, second full paragraph). Thus, the claimed stabilizer is equivalent to the teachings of Hansen in view of Kirk-Othmer.

### **III. Conclusion**

**THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

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the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shawquia Young whose telephone number is 571-272-9043. The examiner can normally be reached on 7:00 AM-3:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Shawquia Young/

Examiner, Art Unit 1626

/Rebecca L Anderson/

Primary Examiner, Art Unit 1626

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